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(54) Title: RESIN PARTICLE, MEDICAL MATERIAL AND PHARMACEUTICAL PREPARATION CONTAINING SAID RESIN PARTICLE

(57) Abstract

A resin particle is provided which comprises an ethylene vinyl alcohol copolymer and 5 to 90 % by weight of cilostazol incorporated therein, and has a particle size of not greater than 2,000 μm. The resin particle, upon being administered orally, allows the concentration of cilostazol in blood to be kept constant over an extended period of time and, therefore, remarkably alleviates side effects such as pain and headache which may otherwise be caused by rapid release of cilostazol into a body.

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DESCRIPTION

RESIN PARTICLE, MEDICAL MATERIAL AND PHARMACEUTICAL PREPARATION CONTAINING SAID RESIN PARTICLE

TECHNICAL FIELD

The present invention relates to a resin particle containing cilostazol as an active ingredient, a medical material and a pharmaceutical preparation containing said resin particle, which is particularly used as an oral preparation.

BACKGROUND ART

Cilostazol exhibits a high thrombocyto-aggregation inhibiting action as well as a phosphodiesterase inhibiting action, anti-ulcerative action, depression action and resolution action. Therefore, cilostazol is widely used as an anti-thrombotic agent, cerebrovascular agent, anti-inflammatory agent, anti-hypertensive agent, anti-asthma agent and phosphodiesterase inhibitor.

Cilostazol is typically admixed with an excipient and other ingredients and compressed into a tablet form for oral administration.

Since the tablet rapidly disintegrates upon being administered orally, an undesirably large amount of cilostazol is released in a body in a short time, thereby causing side effects such as headache, heavy head feeling and pain.

DISCLOSURE OF INVENTION

To solve the aforesaid problem, it is a principal

object of the present invention to provide a resin particle which is capable of continuously releasing a required amount of cilostazol in a body over an extended period of time.

The present inventors have been studied the incorporation of cilostazol in a polymer material to solve the aforesaid problem, and found that a resin particle prepared by incorporating 5 to 90% by weight of cilostazol into an ethylene vinyl alcohol copolymer and granulating the resulting resin into a particle size of not greater than 2,000μm can release cilostazol into a body at a controlled rate, thereby ensuring the continuous release of cilostazol into the body over an extended period of time. Thus, the inventors have achieved the present invention.

In accordance with the present invention, there is provided a resin particle comprising an ethylene vinyl alcohol copolymer and a cilostazol incorporated therein, the cilostazol being contained in an amount of 5 to 90% by weight for the total amount of the ethylene vinyl alcohol copolymer and the cilostazol, the resin particle having particle size of not greater than 2,000μm.

The ethylene vinyl alcohol copolymer is highly stable and biologically safe, and is used in various medical materials. Cilostazol is highly dispersible in the ethylene vinyl alcohol copolymer. Therefore, cilostazol is incorporated in the ethylene vinyl alcohol copolymer in a

desired proportion at a high temperature, and then the resulting resin is cooled into a solid state. Alternatively, cilostazol and the ethylene vinyl alcohol copolymer are dissolved in a solvent, and then the solvent is removed from the resulting solution to obtain a solid resin.

The medical material of the present invention comprises an ethylene vinyl alcohol copolymer and 60 to 85% by weight of cilostazol incorporated therein.

The resin particle of the present invention is used singly or in combination with a pharmaceutically available carrier as a pharmaceutical preparation.

BEST MODE FOR CARRYING OUT THE INVENTION

The ethylene content in the ethylene vinyl alcohol copolymer is appropriately determined depending on the processing method of the resin particle, but may be generally 27 to 70 mol.%, preferably 38 to 47 mol.%, most preferably 44 to 47 mol.%. An ethylene content of less than 27 mol.% will result in a poor processibility of the ethylene vinyl alcohol copolymer by a melting method which will be described later. On the other hand, an ethylene content of greater than 70 mol.% will result in a poor miscibility of cilostazol with the ethylene vinyl alcohol copolymer.

The ethylene vinyl alcohol copolymer has a number-average degree of polymerization of 5,000 to 100,000, preferably 10,000 to 50,000, more preferably 12,000 to 40,000.

As required, any of various biologically safe plasticizers, stabilizers, secondary plasticizers, lubricants and like additives may be added to the ethylene vinyl alcohol copolymer.

The ethylene vinyl alcohol copolymer generally has a melting point of 120 to 200°C, preferably 140 to 191°C, most preferably 160 to 175°C. A melting point of lower than 120°C will result in a poor solubility and dispersibility of cilostazol in the ethylene vinyl alcohol copolymer. A melting point of higher than 200°C will cause the decomposition of cilostazol, resulting in a poor processibility of the ethylene vinyl alcohol copolymer and the coloration of the ethylene vinyl alcohol copolymer during the melting process.

The content of cilostazol is generally about 5 to 90% by weight, preferably 20 to 85% by weight, more preferably 30 to 85% by weight, where 40 to 85% by weight is preferred and 60 to 85% by weight is most preferred. If the content of cilostazol is less than 5% by weight, desired absorption of cilostazol through oral administration cannot be expected because of excessive release of cilostazol. If the content of cilostazol is greater than 90% by weight, the sustained-release effect is not recognized so that suppression of side effects such as headache cannot be expected.

The particle size of the resin particle containing cilostazol is not greater than 2,000μm, preferably not greater

than 1,000μm, most preferably not greater than 600μm. More specifically, the particle size is in a range of 75 to 250μm, wherein 75 to 150μm is preferred and 75 to 105μm is most preferred. A particle size of greater than 2,000μm is inappropriate, because the release of cilostazol from the inside of particles is excessively suppressed, failing to obtain a desired absorption of cilostazol through oral administration.

To prepare the resin particle of the present invention, the melting method is preferably employed in which cilostazol is admixed with the ethylene vinyl alcohol copolymer in a molten state and the resulting melt is formed into a predetermined form. Cilostazol should be homogeneously dispersed in the ethylene vinyl alcohol copolymer without being decomposed during the melting process. For this, the ethylene vinyl alcohol copolymer is melted at a temperature lower than the decomposition point of cilostazol (about 240°C), generally 140 to 210°C, preferably 160 to 185°C, most preferably 165 to 180°C. As required, the melting and forming processes are performed in an oxygen-free atmosphere to prevent the cilostazol and the copolymer from being oxidized. Moisture contained in the ethylene vinyl alcohol copolymer is preferably removed as much as possible to ensure the stability of the cilostazol and the copolymer and the integrity of the formed resin particle.

Any of various melt forming methods can be employed. For example, the melt is formed into a bar shape, drop shape or sheet form by extrusion. Injection molding may otherwise be employed.

After the forming, the resin particle is ground by a grinder and, as required, the resulting particles are sieved to obtain a predetermined particle size. The grinder and grinding conditions to be employed may be appropriately determined depending on a desired particle size and the like.

The release of cilostazol from the resin particle formed through the melt forming process can be controlled by appropriately adjusting the content of cilostazol in the resin particle, and the saponification value of and the ethylene content in the ethylene vinyl alcohol copolymer. The release of cilostazol can otherwise be controlled by adding, as required, a plasticizer, stabilizer, secondary plasticizer, lubricant and a like additive to the ethylene vinyl alcohol copolymer.

Instead of the melt method, a solution method may be employed. In the solution method, the ethylene vinyl alcohol copolymer and cilostazol are homogeneously dissolved in a solvent, and then the solvent is removed from the solution. The resulting resin is ground in the same manner as described above to obtain the resin particle of the present invention.

Examples of the solvent include dimethylformamide,

dimethylacetamide, dimethyl sulfoxide, cyclohexanone, tetrahydrofuran, chloroform, dichloromethane, acetone and 1,1,1,3,3,3-hexafluoro-2-propanol. The aforesaid solvents are used either alone or in combination. Among the aforesaid solvents, 1,1,1,3,3,3-hexafluoro-2-propanol and dimethyl sulfoxide are particularly preferable because the ethylene vinyl alcohol copolymer is highly soluble therein and these solvents can be easily removed by evaporation.

Contaminants in the ethylene vinyl alcohol copolymer to be used are preferably preliminarily removed therefrom through sufficient cleaning by means of Soxhlet's extractor. Further, moisture in the copolymer is preferably perfectly removed therefrom by sufficient drying.

The solution containing the aforesaid ingredients dissolved therein is spread onto a glass plate or extruded in a bar form, and then the solvent is removed from the solution. Thus, the resin particle can be obtained in a film form or bar form. The removal of the solvent is achieved by, for example, air drying, heat drying under a reduced pressure, or phase separation by adding a solidifying agent to the solution. Examples of the solidifying agent include poor solvents for the ethylene vinyl alcohol copolymer, for example, water, alcohols such as methanol, ethanol, propanol and butanol, and ketones such as acetone. In this case, the diffusion of cilostazol into the solidifying agent during the

solidification process should be prevented as much as possible. Therefore, where the solubility of cilostazol in such a poor solvent is high, another solvent is preferably added to the poor solvent to reduce the solubility of cilostazol in the solidifying agent.

The release of cilostazol from the resin particle formed by the solution method can be controlled by appropriately adjusting the amount of cilostazol to be incorporated in the ethylene vinyl alcohol copolymer and the ethylene content in the ethylene vinyl alcohol copolymer, and by appropriately selecting the solvent removing method (e.g., drying under atmospheric pressure or under reduced pressure, or solidification using the solidifying agent). The release rate of cilostazol can otherwise be controlled by adding, as required, a plasticizer, stabilizer, secondary plasticizer, lubricant and a like additive to the ethylene vinyl alcohol copolymer.

The resin particle containing cilostazol can be orally administered to animals or human beings directly or in any of various formulations such as capsule, tablet, granules and suspension which are obtained by mixing the resin particle with a pharmaceutically available carrier. The resin particle may otherwise be administered in a suppository formulation.

Formulations such as tablet and capsule for oral administration are prepared in a conventional manner. More

specifically, the resin particle of the present invention is mixed with an excipient such as gelatin, starch, lactose, magnesium stearate, talc or gum arabic, and the resulting mixture is compressed into a tablet form. Alternatively, the resin particle is mixed with an inert filler, diluent or the like, and the resulting mixture is filled in a hard gelatin capsule or soft capsule.

The amount of the resin particle to be administered is not particularly limited, but may be appropriately selected from a wide range. To produce a primary effect of cilostazol, the dose of cilostazol is preferably 0.06 to 10mg/1kg-weight per day. The formulation preferably contains 1 to 500mg of the resin particle and may be administered once a day.

The medical material of the present invention is suitable for use as, for example, materials for pharmaceutical preparation or medical device which are capable of continuously releasing cilostazol in an effective concentration. The medical material can also be provided in medical devices (e.g., platelet bags, extracorporeal circulation circuits) to achieve antiplatelet action.

FIELD OF INDUSTRIAL APPLICABILITY

The resin particle of the present invention comprises particles of an ethylene vinyl alcohol copolymer and cilostazol incorporated therein in a predetermined proportion, and has a predetermined particle size. The release of

cilostazol into a body is suppressed to keep the cilostazol concentration in blood constant over an extended period of time. Therefore, side effects such as pain and headache can be remarkably alleviated which may otherwise be caused by rapid release of cilostazol into the body.

The medical material of the present contributes to the continuous release of cilostazol in an effective concentration.

EXAMPLES

EXAMPLE 1

A mixture of 60g of cilostazol and 60g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 165°C by means of a mixing extruder (CS-194A available from Custom Scientific Instruments Inc.). The extruded resin particle was ground by means of a small-scale grinder (SM-1 available from Iuchiseieido). Thus, particles containing 50% by weight of cilostazol were obtained.

EXAMPLE 2

The particles (containing 50% by weight of cilostazol) obtained in EXAMPLE 1 were classified into particle size ranges of 355 to 500μm, 250 to 355μm, 150 to 250μm, 105 to 150μm, 75 to 105μm, less than 75μm, and the

other by using sieves specified by JIS (Japanese Industrial Standards).

EXAMPLE 3

Particles containing 40% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 48g of cilostazol and 72g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 165°C.

EXAMPLE 4

The particles (containing 40% by weight of cilostazol) obtained in EXAMPLE 3 were classified into particle size ranges of 105 to 150μm, 75 to 105μm, less than 75μm, and the other.

EXAMPLE 5

Particles containing 30% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 36g of cilostazol and 84g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 165°C.

EXAMPLE 6

The particles (containing 30% by weight of

cilostazol) obtained in EXAMPLE 5 were classified into particle size ranges of 105 to 150μm, 75 to 105μm, less than 75μm, and the other.

EXAMPLE 7

Particles containing 20% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 24g of cilostazol and 96g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 165°C.

EXAMPLE 8

Particles containing 10% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 12g of cilostazol and 108g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 165°C.

EXAMPLE 9

Particles containing 5% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 6g of cilostazol and 114g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a

ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 165°C.

EXAMPLE 10

Particles containing 60% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 72g of cilostazol and 48g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 165°C.

EXAMPLE 11

The particles (containing 60% by weight of cilostazol) obtained in EXAMPLE 10 were classified into particle size ranges of 75 to 105μm, less than 75μm, and the other.

EXAMPLE 12

Particles containing 70% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 84g of cilostazol and 36g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 170°C.

EXAMPLE 13

The particles (containing 70% by weight of

cilostazol) obtained in EXAMPLE 12 were classified into particle size ranges of 75 to 105μm, less than 75μm, and the other.

EXAMPLE 14

Particles containing 80% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 96g of cilostazol and 24g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 170°C.

EXAMPLE 15

The particles (containing 80% by weight of cilostazol) obtained in EXAMPLE 14 were classified into particle size ranges of 75 to 105μm, less than 75μm, and the other.

EXAMPLE 16

Particles containing 90% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 108g of cilostazol and 12g of an ethylene vinyl alcohol copolymer (EVAL ES-G 110A available from Kuraray Co., Ltd., ethylene content: 47 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 170°C.

EXAMPLE 17

The particles (containing 90% by weight of cilostazol) obtained in EXAMPLE 16 were classified into particle size ranges of less than 75μm and the other.

EXAMPLE 18

Particles containing 40% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 48g of cilostazol and 72g of an ethylene vinyl alcohol copolymer (EVAL EP-E 105A available from Kuraray Co., Ltd., ethylene content: 44 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 170°C.

EXAMPLE 19

The particles (containing 40% by weight of cilostazol) obtained in EXAMPLE 18 were classified into particle size ranges of 75 to 105μm and the other.

EXAMPLE 20

Particles containing 50% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 60g of cilostazol and 60g of an ethylene vinyl alcohol copolymer (EVAL EP-E 105A available from Kuraray Co., Ltd., ethylene content: 44 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 170°C.

EXAMPLE 21

The particles (containing 50% by weight of

cilostazol) obtained in EXAMPLE 20 were classified into particle size ranges of 75 to 105μm and the other.

EXAMPLE 22

Particles containing 60% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 72g of cilostazol and 48g of an ethylene vinyl alcohol copolymer (EVAL EP-E 105A available from Kuraray Co., Ltd., ethylene content: 44 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 170°C.

EXAMPLE 23

The particles (containing 60% by weight of cilostazol) obtained in EXAMPLE 22 were classified into particle size ranges of 75 to 105μm and the other.

EXAMPLE 24

Particles containing 70% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 84g of cilostazol and 36g of an ethylene vinyl alcohol copolymer (EVAL EP-E 105A available from Kuraray Co., Ltd., ethylene content: 44 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 175°C.

EXAMPLE 25

The particles (containing 70% by weight of cilostazol) obtained in EXAMPLE 24 were classified into

particle size ranges of 75 to 105μm and the other.

EXAMPLE 26

Particles containing 80% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 96g of cilostazol and 24g of an ethylene vinyl alcohol copolymer (EVAL EP-E 105A available from Kuraray Co., Ltd., ethylene content: 44 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 175°C.

EXAMPLE 27

The particles (containing 80% by weight of cilostazol) obtained in EXAMPLE 26 were classified into particle size ranges of 75 to 105μm and the other.

EXAMPLE 28

Particles containing 90% by weight of cilostazol were obtained in substantially the same manner as in EXAMPLE 1, except that a mixture of 108g of cilostazol and 12g of an ethylene vinyl alcohol copolymer (EVAL EP-E 105A available from Kuraray Co., Ltd., ethylene content: 44 mol.%) in a ground form (sieved with a 28-mesh) was melted and extruded at an extruding temperature of 175°C.

EXAMPLE 29

The particles (containing 90% by weight of cilostazol) obtained in EXAMPLE 28 were classified into particle size ranges of 75 to 105μm and the other.

RELEASE TEST

The particles obtained in each of EXAMPLES 1 to 29 in an amount equivalent to a cilostazol content of 50mg were immersed in a 500-ml test solution (0.3% sodium lauryl sulfate solution), and the amount of cilostazol released into the test solution was determined by the absorption photometry at predetermined time intervals. The results are shown in Table 1.

Table 1

Release of cilostazol(wt.%)

Example		Time lapse (hr) 1	2	3	4	6	8	10	12
1		28	35	40	44	49	53	57	60
2	355-500 μm p.s.	9	14	16	18	22	26	29	31
	250-355 μm p.s.	13	18	23	25	29	32	36	39
	150-250 μm p.s.	19	27	33	37	42	49	53	57
	105-150 μm p.s.	31	42	48	53	61	67	71	75
	75-105 μm p.s.	42	54	60	66	74	78	84	84
	< 75 μm p.s.	67	79	85	89	94	97	99	100
3		10	14	17	19	24	27	29	33
4	105-150 μm p.s.	17	22	27	31	36	40	45	49
	75-105 μm p.s.	21	29	34	40	46	51	56	61
	< 75 μm p.s.	35	44	52	58	66	70	75	80
5		9	12	15	19	21	23	27	29
6	105-150 μm p.s.	16	22	28	31	38	43	47	52
	75-105 μm p.s.	21	31	37	42	49	57	60	66
	< 75 μm p.s.	36	49	56	66	72	79	84	86
7		7	8	10	11	14	15	18	19
8		8	13	16	20	22	24	28	30
9		7	12	15	16	20	22	26	27
11	75-105 μm p.s.	26	36	42	47	55	59	63	67
	< 75 μm p.s.	48	60	66	71	78	83	86	89
13	75-105 μm p.s.	39	53	61	67	76	83	86	89
	< 75 μm p.s.	73	83	88	91	95	97	98	100
15	75-105 μm p.s.	52	70	79	86	93	98	100	102
	< 75 μm p.s.	81	92	97	97	101	102	103	104
17	< 75 μm p.s.	81	89	91	92	93	94	95	95
19	75-105 μm p.s.	25	33	39	43	50	55	58	61
21	75-105 μm p.s.	31	41	47	52	59	64	69	72
23	75-105 μm p.s.	27	37	45	50	59	65	69	72
25	75-105 μm p.s.	38	51	62	66	75	82	86	88
27	75-105 μm p.s.	50	70	79	87	93	97	99	99
29	75-105 μm p.s.	64	83	93	100	99	102	102	100

"p.s." means "particle size"

As can be seen from Table 1, the release of cilostazol can be controlled as desired by appropriately selecting the cilostazol content and particle size.

ABSORPTION TEST

An absorption test was carried out on the following test preparations and control preparation.

Test preparation 1: Particles having a particle size range of 75 to 105μm obtained in EXAMPLE 2

Test preparation 2: Particles having a particle size range of 75 to 105μm obtained in EXAMPLE 4

Test preparation 3: Particles having a particle size range of 75 to 105μm obtained in EXAMPLE 19

Test preparation 4: Particles having a particle size range of 75 to 105μm obtained in EXAMPLE 21

Control preparation: Hydroxypropyl methyl cellulose (HPMC) suspension containing 10mg of cilostazol

The test preparations and the control preparation each containing 10mg of cilostazol were respectively filled in minicapsules for rats to be used in the absorption test. The preparations were orally administered to rats (32 rats for each test group), and blood was sampled from inferior vena cava of each rat after 0.5, 1, 2, 3, 4, 6, 8, 10 hours (n=4). Then, cilostazol concentrations in sera of the respective blood samples were determined by the rapid liquid chromatography, and the degrees of cilostazol absorption were compared with each other. The results are shown in Table 2.

Table 2

Cilostazol concentration in blood serum (ng/ml)

	Time lapse (hr)							
	0.5	1	2	3	4	6	8	10
Test Preparation 1	14	25	53	48	49	40	15	18
Test Preparation 2	16	23	46	75	32	60	32	30
Test Preparation 3	7	6	11	80	38	48	40	19
Test Preparation 4	12	11	35	21	51	55	41	30
Control Preparation	73	96	148	107	83	30	6	11

As can be seen from Table 2, a rapid increase in the cilostazol concentration in blood serum immediately after the administration of each of the test preparations is suppressed in comparison with the control preparation. The cilostazol concentration is kept high even after six hours. This indicates that the maximum cilostazol concentration in blood serum (Cmax) can be lowered and, at the same time, the serum cilostazol concentration is maintained in a desired range over an extended period of time.

Pharmaceutical Example 1

A 200mg of the particles obtained in EXAMPLE 2 (which contains 50% by weight of cilostazol and has a particle size of 75 to 105μm) were filled in a capsule to give a capsule containing 100mg of cilostazol.

Pharmaceutical Example 2

A 125g of the particles obtained in EXAMPLE 27 (containing 80% by weight of cilostazol, particle size of 75 to 105μm), 40g of crystal cellulose, 34g of corn starch and 1g of magnesium stearate were milled together. The resulting mixture was tableted by means of an R 9-mm punch to give a 200mg tablet containing 100mg of cilostazol.

CLAIMS

1. A resin particle comprising an ethylene vinyl alcohol copolymer and a cilostazol incorporated therein, the cilostazol being contained in an amount of 5 to 90% by weight for the total amount of the ethylene vinyl alcohol copolymer and the cilostazol, the resin particle having particle size of not greater than 2,000μm.

2. A resin particle as set forth in claim 1, wherein cilostazol is contained in an amount of 20 to 85% by weight.

3. A resin particle as set forth in claim 2, wherein cilostazol is contained in an amount of 30 to 85% by weight.

4. A resin particle as set forth in claim 3, wherein cilostazol is contained in an amount of 40 to 85% by weight.

5. A resin particle as set forth in claim 4, wherein cilostazol is contained in an amount of 60 to 85% by weight.

6. A resin particle as set forth in claim 5, wherein a particle size of the resin particle is not greater than 600μm.

7. A resin particle as set forth in claim 6, wherein a particle size of the resin particle is in a range of 75 to 250μm.

8. A resin particle as set forth in claim 7, wherein a particle size of the resin particle is in a range of 75 to 150μm.

9. A resin particle as set forth in claim 8, wherein a particle size of the resin particle is in a range of 75 to

105μm.

10. A resin particle as set forth in claim 4, wherein a particle size of the resin particle is not greater than 600μm.

11. A resin particle as set forth in claim 10, wherein a particle size of the resin particle is in a range of 75 to 250μm.

12. A resin particle as set forth in claim 11, wherein a particle size of the resin particle is in a range of 75 to 105μm.

13. A resin particle as set forth in claim 1, wherein cilostazol and ethylene vinyl alcohol copolymer are blended in a molten state.

14. A resin particle as set forth in claim 13, wherein a melting temperature is 165 to 180°C.

15. A resin particle as set forth in claim 14, wherein cilostazol is contained in an amount of 60 to 85% by weight.

16. A resin particle as set forth in claim 15, wherein ethylene is contained in an amount of 44 to 47 mol.% in the ethylene vinyl alcohol copolymer.

17. A resin particle as set forth in claim 16, wherein a number-average degree of polymerization of the ethylene vinyl alcohol copolymer is in a range of 12,000 to 40,000.

18. A medical material comprising an ethylene vinyl alcohol copolymer and a cilostazol incorporated therein, the cilostazol being contained in an amount of 60 to 85% by weight

for the total amount of the ethylene vinyl alcohol copolymer and the cilostazol.

19. A medical material as set forth in claim 18, wherein a melting temperature is in a range of 165 to 180°C.

20. A medical material as set forth in claim 19, wherein ethylene is contained in an amount of 44 to 47 mol % in the ethylene vinyl alcohol copolymer.

21. A medical material as set forth in claim 20, wherein a number-average degree to polymerization of the ethylene vinyl alcohol copolymer is in a range of 12,000 to 40,000.

22. A medical material as set forth in claim 21, wherein ethylene is contained in a range of 38 to 47 mol.% in the ethylene vinyl alcohol copolymer.

23. A medical material as set forth in claim 22, wherein a number-average degree of polymerization of the ethylene vinyl alcohol copolymer is in a range of 12,000 to 40,000.

24. A pharmaceutical preparation comprising a resin particle as set forth in claim 1, or a mixture of the resin particle and a pharmaceutically available carrier.

INTERNATIONAL SEARCH REPORT

Intern[illegible] Application No PCT/JP 96/00004

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 31/47,9/14,9/22

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A, 94/14 444 (OTSUKA PHARMACEUTICAL CO., LTD.) 07 July 1994 (07.07.94), abstract. --	1-17, 24
A,P	CHEMICAL ABSTRACTS, vol. 123, no. 8, issued 1995, August 21 (Columbus, Ohio, USA) M. KIMURA et al. "Pharmaceutical compositions containing carbostyryl derivatives for endothelial cell damage", page 701, column 2, no. 93 263j; & JP,A,07 076 584 (JPN. KOKAI TOKKYO KOHO). --	1-17, 24

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
26 February 1996	26.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	MAZZUCCO e.h.

Form PCT ISA/210 (second sheet) (July 1992)

C(continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 116, no. 23, issued 1992, June 08 (Columbus, Ohio, USA) G. YOSHINO "Pharmaceuticals containing carbostyril derivatives for prevention and treatment of hyperlipemia", page 86, column 2, no. 228 261k; & JP,A,04 005 233 (JPN. KOKAI TOKKYO KOHO). --	1-17, 24
A	CHEMICAL ABSTRACTS, vol. 117, issued 1992, October 19 (Columbus, Ohio, USA) S. AZUMA et al. " Pharmaceuticals for treatment of diabetic nerve disorders", page 450, column 1, no. 157 663a; & JP,A, 04 159 224 (JPN. KOKAI TOKKYO KOHO JP). --	1-17, 24
A	CH, A, 683 673 (OTSUKA PHARMACEUTICAL FACTORY, INC.) 29 April 1994 (29.04.94), abstract; claims 1,9-12. ----	1,18